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Understanding variability in the ErbB signaling network.

Short Abstract — We describe a systems approach to combine mathematical modeling and experimental measurement in the study of signal transduction in mammalian cells. Our focus is on the epidermal growth factor receptor (EGFR) family and downstream signaling pathways. EGFR networks are prototypical cue-signal-response pathways of high biomedical importance. Construction of mathematical signal transduction models that recapitulate key features of signaling pathways as they exist in cells is currently very difficult, in large part because few tools are available to assemble, validate and update large dynamical models. The dissemination and composition of such models is also difficult. We illustrate the development, implementation, and deployment of a new approach based on "rules-based" modeling, using rules as an algorithmic framework for modeling.

***Keywords* — ErbB, EGFR, rules-based modeling, ODE, reaction networks, signaling.**

I. Purpose

THE consensus view of the ErbB network reveals a series of overlapping and interacting pathways of considerable complexity [i,ii,iii] Our challenge is to translate the underlying data describing these complex pathways into a formal model, based on chemical reaction and dynamical systems theory. Modeling of ErbB and similar pathways has focused on mass-action kinetics within a continuum framework, as represented by set of coupled ordinary differential equations (ODEs). Individual reactions are deduced from the literature converted into a list of equations, which rapidly become large an unwieldy; sets of 500 or more reactions with similar numbers of free parameters are not uncommon. Large reaction networks are inherently difficult to understand and cannot easily be formally checked for accuracy. The problem gets substantially worse when it becomes necessary to alter the topology of the network in the face of new data, or to model alternative hypotheses. Changes are traditionally made by rewriting the ODE networks piece by piece, an error-prone process that requires near perfect bookkeeping. Calibration of models to experimental data, model analysis and the dissemination of key findings are equally daunting. Thus, before the benefits of formal modeling can be realized, substantial limitations in methodology need to be overcome.

Very recently several possible solutions to the problem of managing complex models have emerged, based on the use of programs or meta-languages that describe pathways at a higher level of abstraction. One promising approach, "rules-based" modeling, uses a meta-language to describe topology of networks in terms of the reactions in which individual components can participate[iv,v,vi,vii] Rules are combined to create an abstracted logical representation of a network that can then be instantiated in a number of ways, including an ODE network. Specialized software, in which rules are written, acts as an intermediate between the user and the mathematical description of the reaction network. The software can link rules together in different ways, and check the links for logical consistency. The advantages of this approach include much greater flexibility in adding, modifying or deleting paths or species in the network, and the possibility of automatically creating sets of models with different topologies. However, rules-based modeling is still in its infancy and has not yet been evaluated critically for its ability to assemble models that incorporate substantial experimental data.

Large models are also difficult to analyze for mechanistic insight that can be disseminated to the larger research community. Rules based modeling promises to add new analytic tools including agent-based representations and standard for model composition (that is, combining two or model models into one). However, rules-based approaches are not in and of themselves a sufficient solution. A significant part of our lab activity is therefore attempting to develop methods for model annotation and sharing based on semantic web approaches.[viii] A combination of rules-based modeling and semantic web infrastructures seems a particularly promising but as yet unexplored avenue.

This paper presents our progress in the implementation of a rules-based approach to models of the ErbB signaling network, calibration of these models against diverse data obtained from human tumor cells, and generation of predictions that will then be subjected to experimental verification.

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